의학석사 학위 논문

Hashimoto thyroiditis is associated with the efficacy of low dose (30 mCi) radioiodine ablation in differentiated thyroid cancer.

하시모토 갑상선염이 30 mCi 저용량 방사선요오드 잔여 갑상선 제거술에 미치는 영향

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Hashimoto thyroiditis is associated with the efficacy of low dose (30 mCi) radioiodine ablation in differentiated thyroid cancer.

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Abstract

Background: Radioactive iodine (RAI) ablation is considered in the postsurgical management of differentiated thyroid carcinoma (DTC). The aim of this study was to investigate the effectiveness of low dose (30 mCi) RAI ablation and the factors associated with RAI success.

Methods: A retrospective study was conducted on 691 patients who received low dose RAI ablation after total thyroidectomy. The success of the first RAI ablation was defined as no remnant on the whole body scan with preablative stimulated thyroglobulin (s-Tg) <2.0ng/ml at the second time of RAI administration. Patient demographics, pathologic features, laboratory test, and RAI ablation result were collected.

Results: Low dose RAI ablation was successful in 431 patients (62.3%) after the first RAI therapy. The first RAI failure was associated with multiplicity (39.3% vs 47.1%, p=0.045) and bilaterality (23.1% vs 30.1%, p=0.041) of primary tumor, coexisting Hashimoto thyroiditis (HT; 25.5% vs 40.8%, p<0.001), and higher s-Tg level (1.5±2.4 vs 6.5±19.0, p<0.001). There were no significant differences in age, sex, and pathologic features of tumor including size.

On multivariate analyses, both coexisting HT and preablative s-Tg retained

statistical significance. The relative risk (RR) of first RAI failure with coexisting HT was significantly increased at 2.86 (95% confidence interval [CI] 1.95, 4.17, $p<0.001$). The RR along preablative s-Tg level was also increased, with an RR of 1.23 (95% CI 1.15, 1.31, $p<0.001$).

Conclusions: Success of low dose RAI ablation at the first time was influenced by coexisting HT. Further investigation about the relation of HT and RAI ablation is warranted.

Keywords: radioiodine, ablation, low dose, Hashimoto thyroiditis

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List of Abbreviations

DTC	**differentiated thyroid carcinoma**
HT	**Hashimoto thyroiditis**
LN	**lymph node**
RAI	**radioactive iodine**
RR	**relative risk**
s-Tg	**stimulated thyroglobulin**
Tg	**thyroglobulin**
TgAb	**thyroglobulin antibody**
TSH	**thyroid stimulating hormone**
WBS	**whole-body scan**

Introduction

Radioactive iodine (RAI) ablation after total thyroidectomy is usually considered for patients with differentiated thyroid carcinoma (DTC). Ablation of the small amount of residual normal thyroid may facilitate the early detection of recurrence based on serum thyroglobulin measurement and/or RAI whole body scan (WBS).[1] The post-RAI scan obtained at the time of remnant ablation may influence initial staging by identifying previously undiagnosed disease, especially in the lateral neck. Furthermore, from a theoretical point of view, this first dose of RAI may also be considered adjuvant therapy because of the potential tumoricidal effect on persistent thyroid cancer cells remaining after appropriate surgery in patients at risk for recurrence or disease specific mortality.

According to the American thyroid association guideline, RAI ablation is recommended for 1) all patients with gross extrathyroidal extension or primary tumor size > 4cm, and 2) selected patients with 1-4cm thyroid cancers confined to the thyroid, lymph node (LN) metastases, or other higher risk features.[1] No specific amount of activity is preferred, and the recommendation is to use "the minimum activity (30-100 mCi) necessary to achieve successful remnant ablation."

There are several advantages to both the patient and healthcare provider for using a lower activity of RAI, including less time in isolation, a shorter hospital stay, reduced exposure of RAI to the environment, and lower financial cost.[2] Furthermore, RAI ablation is associated with an increased risk of second primary malignancies;

the lower the activity administered the lower the risk.[3] However, there are some controversies whether low dose RAI is feasible to all DTC patients. The aim of this study was to investigate the effectiveness of low dose (30 mCi) RAI ablation and the factors associated with RAI success.

Methods

From August 2004 to July 2012, a total of 738 patients with DTC underwent total thyroidectomy received low dose RAI ablation in Seoul National University Bundang Hospital. After we reviewed all patients in this cohort, we excluded 47 patients: 42 with a thyroid stimulating hormone (TSH) below 30mIU/L at the first or second time of ablation, 3 with missing preablative laboratory tests, and 2 in whom LN dissection was performed between the first and second RAI ablation.

In the study population of 691 patients, a WBS using 1110 MBq (30 mCi) of ^{131}I and stimulated thyroglobulin (s-Tg) measurement was performed two or three months after surgery. A second dose was given 6-12 months after the first low dose. The success of the first RAI ablation was defined as no remnant on the WBS with low serum s-Tg (< 2.0ng/ml) at the second time of RAI administration.

One hundred three patients with high thyroglobulin antibody (≥ 150 uU/ml) were identified when a thyroglobulin antibody (TgAb) level < 150 uU/ml was considered as negative interference. To exclude the possible interference of the TgAb, subgroup analysis was performed in the low TgAb (< 150 uU/ml) patients.

Patient demographics, pathologic features, laboratory test, and RAI ablation result were collected.

Results

At the time of the first RAI ablation, mean patient age was 47.8 ± 10.5 years and female-to-male ratio was 4 : 1 (Table 1). Total thyroidectomy without lymph node (LN) dissection was performed in 18.2% (126/691) of patients and 81.7% of patients underwent combined central LN dissection. Mean tumor size was 1.19 ± 0.94 cm and extrathyroidal extension was found in 69.1% of tumors. LN metastasis was associated with 42.3% of patients. Preablative TSH, s-Tg, and TgAb level were 132.5 ± 75.1 uU/ml, 3.3 ± 12.0 ng/ml, and 89.7 ± 166.7 IU/ml, respectively.

Table 2 showed clinicopathological features of the first RAI success and failure group. The first low dose RAI ablation was successful in 431 (62.3%) patients. Two hundred sixty patients showed remnant thyroid activity on the second WBS and/or high serum s-Tg level after the first RAI ablation. On univariate analysis, the first low dose RAI success was associated with multiplicity (39.3% vs 47.1%, p=0.045) and bilaterality (23.1% vs 30.1%, p=0.041) of primary tumor. Coexisting Hashimoto thyroiditis (HT; 25.5% vs 40.8%, p<0.001) in the pathologic exam was related to the lower rate of successful RAI ablation. Also, preablative s-Tg level was significantly lower in the first RAI success group than the first RAI failure group (1.5 ± 2.4 vs 6.5 ± 19.0, p<0.001). There were no significant differences in age, sex, and pathologic features of tumor including size.

Table 1 Patient characteristics

Characteristics	
Sex (male : female)	138 (20.0%) : 553 (80.0%)
Age (years)	47.8±10.5 (range 15–77)
Combined central LN dissection	565/691 (81.8%)
Pathologic features	
Tumor size (cm)	1.19±0.94 (0.2-12.5)
Encapsulation (None/Partial/Complete)	75.5%/14.5%/9.8%
Capsular invasion	46/640 (6.7%)
Lymphatic invasion	82/687 (11.9%)
Vascular invasion	17/687 (2.5%)
Extrathyroidal extension	
None/Microscopic/Macroscopic	30.9%/60.7%/8.4%
Resection margin involvement	40/690 (5.8%)
LN metastasis	292/690 (42.3%)
Multiplicity	291/689 (42.2%)
Bilaterality	177/688 (25.7%)
Coexisting Hashimoto thyroiditis	215/688 (31.3%)
Laboratory findings	
Pre-ablation TSH	132.5±75.1
Stimulated Tg	3.3±12.0
TgAb	89.7±166.7

LN lymph node; *TSH* thyroid stimulating hormone; *Tg* thyroglobulin; *TgAb* thyroglobulin antibody

On multivariate analyses, both coexisting HT and preablative s-Tg retained statistical significance. The relative risk (RR) of first RAI failure with coexisting HT was significantly increased at 2.86 (95% confidence interval [CI] 1.95, 4.17, $p<0.001$). The RR along preablative s-Tg level was also increased, with an RR of 1.23 (95% CI 1.15, 1.31, $p<0.001$).

To exclude the variation of the s-Tg measurement by TgAb, statistical analysis was performed again in low TgAb patients (Table 3). Multivariate analysis showed that prealbative s-Tg (RR 1.23, 95% CI 1.15, 1.31, $p<0.001$) and coexisting HT (RR 2.76, 95% CI 1.79, 4.24, $p<0.001$) were associated with the success of the first RAI ablation. The results of low TgAb group were similar to that in the all TgAb group.

Table 2 Comparison of 1st low dose RAI success group and failure group

Characteristics	1st group (n=431)	≥2nd group (n=260)	*P* value
Sex (% of female)	81.4	77.7	0.233
Age (years)	48.3±10.4	47.1±10.6	0.149
Combined central LN dissection (%)	83.1	79.6	0.256
Pathologic features			
Tumor size (cm)	1.19±0.84	1.20±1.09	0.893
Encapsulation (%)			0.491
None/Partial/Complete	74.5/14.5/11.0	77.0/14.8/8.2	
Capsular invasion	7.5	5.4	0.298
Lymphatic invasion	10.9	13.6	0.293
Vascular invasion	2.8	1.9	0.490
Extrathyroidal extension			0.663
None/Microscopic/Macroscopic	32.1/59.5/8.4	28.8/62.7/8.5	
Resection margin involvement	6.0	5.4	0.718
LN metastasis	42.6	41.9	0.870
Multiplicity	39.3	47.1	0.045
Bilaterality	23.1	30.1	0.041
Coexisting Hashimoto thyroiditis	25.5	40.8	<0.001
Laboratory findings			
Pre-ablation TSH	130.1±76.0	136.3±73.5	0.295
Stimulated Tg	1.5±2.4	6.5±19.0	<0.001
TgAb	82.1±149.8	102.4±191.2	0.146

Table 3 Comparison of 1st low dose RAI success in the low TgAb patients

Characteristics	1st group (n=380)	≥2nd group (n=211)	*P* value
Sex (% of female)	80.3	75.4	0.164
Age (years)	48.4±10.3	47.0±10.8	0.122
Combined central LN dissection (%)	92.1	89.6	0.298
Pathologic features			
Tumor size (cm)	1.17±0.84	1.17±0.87	0.960
Encapsulation (%)			0.503
None/Partial/Complete	73.7/14.6/11.7	76.2/15.2/8.6	
Capsular invasion	8.0	5.2	0.210
Lymphatic invasion	10.8	13.8	0.283
Vascular invasion	2.6	1.9	0.576
Extrathyroidal extension			0.763
None/Microscopic/Macroscopic	31.7/59.6/8.7	29.9/62.6/7.6	
Resection margin involvement	6.1	5.2	0.669
LN metastasis	40.6	46.0	0.209
Multiplicity	38.5	42.5	0.360
Bilaterality	22.7	28.1	0.145
Coexisting Hashimoto thyroiditis	19.9	31.8	0.001
Laboratory findings			
Pre-ablation TSH	126.9±72.8	132.3±71.6	0.391
Stimulated Tg	1.6±2.5	7.7±20.9	<0.001

Discussion

There are some controversies whether low dose RAI ablation is effective to all DTC patients. However, there is no direct evidence that radioiodine ablation of the thyroid remnant reduces the risk of recurrence or death in those with DTC.[2] It could, therefore, be argued that in the absence of such evidence the lowest activity would be appropriate.

The success rates of low and high dose RAI ranged from 10% to 80% and from 50 to 100%, respectively.[4-7] From a meta-analysis performed in 2000, a high dose RAI resulted in 27% increase of RAI success than low dose one.[8] However, most of the success rate estimates from the low activity studies were based on fewer than 50 patients, and the success rate in the two largest studies was approximately 70%.[9, 10] Furthermore, two randomized prospective trials published in 2012 showed that the success rates were similar between low dose and high dose RAI.[11, 12] The success rate of the first low dose RAI was 62.3% in our study, which was in agreement with previous studies.

Many studies have investigated the factors influencing the rate of successful ablation, including postsurgical remnant size, preablative serum thyroglobulin, method of TSH stimulation, and the use of a preablation scan; nevertheless, there were no definitive predictive factors except preablative s-Tg.[2] Not only small sample sizes, but also confounders including retrospective nature of these studies

and lack of blinding would have contributed to the variability in the associated factors. In the present study, we found that preablative s-Tg and coexisting HT were associated with the success of RAI.

To our best knowledge, this is the first report that coexisting HT can be related to the success of RAI. There are some possible explanations how coexisiting HT would have contributed to the failure of the first RAI ablation. First, thyroid tissue with HT scored significantly lower positive sodium-iodide symporter (NIS) membrane staining than normal thyroid tissue.[13] In a recent clinical study, patients with thyroiditis had a median 0.0089% RAI uptake, whereas patients without thyroiditis had a median 0.0180%; although there was no statistical significance.[14] Lower NIS expression can be one of the explanations of the RAI failure in coexisting HT. Second, HT on histology can be frequently associated with thyroglobulin antibody (TgAb) and therefore mistakenly low or undetectable s-Tg.[15] As TgAb disturbed the precise measurement of the s-Tg, we performed subgroup analyses of patients with low TgAb; the association between HT and the first RAI failure was significant in the subgroup analysis.

In conclusion, success of low dose RAI ablation at the first time was influenced by coexisting HT and preablative s-Tg. However, we do not understand the exact mechanism how coexisting HT increases RAI ablation failure. Further investigation about the relation of HT and RAI ablation is warranted.

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국문 초록

서론: 방사선요오드 잔여 갑상선 제거술은 분화 갑상선 암 수술 후 추가적인 치료로 고려된다. 본 연구에서는 저용량 (30 mCi) 방사선요오드 투여에 따른 잔여 갑상선 제거술의 효과를 확인하고, 잔여 갑상선 제거술의 성공과 실패에 관련된 요인을 규명하는 것을 목표로 한다.

대상환자 및 방법: 분화 갑상선 암으로 갑상선 전 절제술을 받은 후, 저용량 방사선요오드 투여를 받은 691명의 환자를 대상으로 후향적 연구를 시행하였다. 첫 회 잔여 갑상선 제거술의 성공은 2회 치료 직전 검사상 혈청 자극 갑상선호르몬 수치가 2.0ng/ml이하이며, 2회 치료 후 전신 스캔에서 잔여 갑상선 조직이 보이지 않는 경우로 정의하였다.

결과: 저용량 방사선요오드 잔여 갑상선 제거술은 431명 (62.3%)의 환자에서 첫 회에 성공한 것으로 나타났다. 단변량 분석을 시행하였을 때, 저용량 방사선요오드 첫 회 투여 시 잔여 갑상선 제거의 실패와 관계된 요인으로 종양의 다중성 (39.3% vs 47.1%, p=0.045), 양측성 (23.1% vs 30.1%, p=0.041), 동반된 하시모토 갑상선염 (25.5% vs 40.8%, p<0.001) 및 방사선요오드 치료 전 자극 갑상선 글로불린 (1.5±2.4 vs

6.5±19.0, p<0.001)과 관련성이 의심되었다. 대상 환자의 나이, 성별 및 종양의 크기를 비롯한 다른 병리학적 인자와의 관련성은 관찰되지 않았다.

다변량 분석을 시행하였을 때, 동반된 하시모토 갑상선염 및 방사선요오드 치료 전 자극 갑상선 글로불린 만이 통계적으로 유의한 것으로 나타났다. 하시모토 갑상선염이 동반되어 있을 때, 상대 위험도는 2.86 배 (95% 신뢰구간, 1.95, 4.17, p<0.001)으로 계산되었다. 방사선요오드 치료 전 자극 갑상선 글로불린에 따르는 상대 위험도는 1.23배로 (95% 신뢰구간, 1.15, 1.31, p<0.001) 나타났다.

결론: 잔여 갑상선 제거를 위한 첫 회의 저용량 방사선요오드 투여의 성공은 하시모토 갑상선염의 동반 유무와 방사선요오드 치료 전 자극 갑상선 글로불린 수치와 관련이 있었다. 하시모토 갑상선염과 방사선요오드 치료의 관계에 대한 추가적인 연구가 필요하다.

주요어: 방사선요오드, 잔여 갑상선 제거술, 저용량, 하시모토 갑상선염

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